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TCRγδ^{+} AND IL4^{+} T CELLS AS BIOMARKERS OF MUCOSAL LESION IN CELIAC DISEASE

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Celiac disease (CD) is a chronic intestinal inflammation caused by intolerance to gluten in genetically predisposed individuals. All CD patients are characterized by the presence of HLA DQ2/DQ risk alleles and anti-tissue transglutaminase antibodies (anti-tTG2 IgA), but they can be divided on the basis of the intestinal damage in overt and potential-CD. Overt-CD patients show an atrophic intestinal mucosa at histological analysis of duodenal biopsy samples, according to the histological Marsh-classification (Marsh type 3 lesion - M3), while potential CD patients are identified by a morphologically normal intestinal mucosa with low or mild lymphocyte infiltration (Marsh type 0 - M0 or type 1 lesion - M1, respectively). Recently, we have observed that the villous atrophy of patients with overt-CD is characterized by an intestinal expansion of TCRγδ+ T cells and a low frequency of IL4 producing T cells compared to the morphologically normal intestinal mucosa of potential-CD patients. The changes in the frequency of these two lymphocyte populations suggest their involvement in the transition from potential to overt-CD.

In order to demonstrate that TCRγδ+ and IL4+ T cells could be novel cell biomarkers for the different CD forms, the phenotype and cytokine production of these two intestinal lymphocyte populations were investigated by flow cytometry in gut biopsies of children with overt- or potential-CD, and in healthy controls. In particular, a multiparametric flow cytometric analysis was performed on two different experimental systems: *in vitro* approach on gluten-raised short-term T cell lines (st-TCLs) and *ex vivo* approach on intestinal cells freshly isolated from the mucosal samples. Moreover, the possible correlations between the intestinal frequency of TCRγδ+ or IL4+ T cells and the disease indices, such as the serum titers of anti-tTG2 IgA and the degree of mucosal lesion, were evaluated in overt and potential-CD patients.

An intestinal expansion of TCRγδ+ T cells combined with a disappearance of IL4+ T cells characterize the transition from potential to overt-CD. More specifically, the frequencies of IL4-producing T cells inversely correlated with TCRγδ+ T cell expansion ($p<0.005$) and with titers of anti-tTG2 IgA antibodies ($p<0.05$). The changes of these cell subsets density strongly correlated with mucosal lesions, according to the histological Marsh-classification, as the transition from M0 to M3 was associated with a significant reduction of IL4+ T cells and increase of TCRγδ+ T cells.

These results identify TCRγδ+ and IL4+ T cells as novel cell biomarkers of mucosal lesion in CD. In clinical practice, their combined detection in the early stages of intestinal inflammation could represent a useful approach to prevent the transition from potential to overt-CD, discriminating among patients with potential-CD those who could develop the typical CD lesion and giving them a gluten-free diet, even in the absence of symptoms.